REMARKS

Claims 12-50, 52-53, 55-56, 58-59, 61-79 are pending in the application. Claims 51, 54, 57, and 60 have been canceled without prejudice or disclaimer. New claims 74-79 have been added. Claims 12-73 are under active consideration.

A new Sequence Listing setting forth a revised sequence of SEQ ID NO:1 is filed concurrently herewith. SEQ ID NO:1 now corresponds to the sequence of native mature human IL-2 disclosed in Figure 2b of U.S. Patent No. 4,738,927, which was cited in the instant application, for example, at page 17, line 13, and incorporated by reference. The Examiner is respectfully requested to enter the Sequence Listing.

Claims 12, 16, 17, 42, and 63 have been amended to make explicit that the methods are directed to treating a subject for a breast cancer. Support for the amendment can be found in the specification, for example, at page 6, lines 17-20; page 28, lines 18-22. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Claims 12, 16, 17, 42, and 63 have been further amended to make explicit that the anti-HER2 antibody or fragment thereof has anti-tumor activity and binds the same epitope as an anti-HER2 antibody selected from the group consisting of 4D5 and 520C9. Support for the amendment can be found in the specification, for example, at page 4, lines 14-19; page 22, lines 11-16; and page 24, lines 3-4. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

In order to expedite prosecution, claims 12, 16, 17, and 42 have been amended to make explicit that the variants of IL-2 have anti-tumor activity. By this amendment, Applicants expressly do not disclaim equivalents of the invention, which could include polypeptides having biological activities in addition to the recited anti-tumor activity. Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Support for the amendment can be found in the specification, for example, at page 4, lines 11-22; page 6, lines 22-31; page 9, lines 27-31; page 12, lines 5-7 and 20-23; page 18, lines 6-10; page 26, lines 24-25. Accordingly, the specification provides adequate support for this amendment. Entry of the amendment is respectfully requested.

Claim 28 has been amended to recite "said variant is des-alanyl-1, serine-125 human interleukin-2." Applicant is amending the claim solely to obtain expeditious allowance of the instant application and not for reasons related to patentability.

Claim 52 has been amended to depend from claim 12 instead of canceled claim 51. Claim 55 has been amended to depend from claim 16 instead of canceled claim 54. Claim 58 has been amended to depend from claim 17 instead of canceled claim 57. Claim 61 has been amended to depend from claim 42 instead of canceled claim 60. Entry of these amendments is respectfully requested.

Claim 71 has been amended to depend from claim 69 in order to clarify antecedent basis.

Claim 72 has been amended to depend from claim 70 in order to clarify antecedent basis.

Support for new claims 74-79 can be found in the specification, for example, at Example 1. Entry of the new claims is therefore respectfully requested.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

35 U.S.C. § 132

The Examiner has objected to the reference to SEQ ID NO:1 in the specification at page 29 and the Sequence Listing, submitted August 5, 2005. In particular, the Office Action alleges that the original disclosure of the specification does not provide descriptive support for the amendment filed August 5, 2005. (Office Action, page 3).

Applicants submit that neither the Sequence Listing nor the previous amendment to the specification included new matter; however, Applicants have submitted a new Sequence Listing setting forth a revised sequence of SEQ ID NO:1 corresponding to the sequence of native mature human IL-2 disclosed in Figure 2b of U.S. Patent No. 4,738,927, which was cited in the instant application, for example, at page 17, line 13, and incorporated by reference. The Examiner is respectfully requested to enter the new Sequence Listing.

The proscription against the introduction of new matter in a patent application (35 U.S.C. 132 and 251) serves to prevent an applicant from adding information that goes beyond the

subject matter originally filed. See, *e.g., In re Rasmussen*, 650 F.2d 1212, 1214, 211 USPQ 323, 326 (CCPA 1981) and MPEP § 2163.06. Further, the claims as filed in the original specification are part of the disclosure. Therefore, if an application as originally filed contains a claim disclosing material not found in the remainder of the specification, the applicant may amend the specification to include the claimed subject matter. *See, e.g., In re Benno*, 768 F.2d 1340, 226 USPQ 683 (Fed. Cir. 1985).

The sequence of human IL-2 was well-known at the time of filing of the instant application and was disclosed in Figure 2b of U.S. Patent No. 4,738,927, which was cited and incorporated by reference in the specification at page 17, line 13. No new matter is added by the revised Sequence Listing. Applicants are merely presenting the sequence of human IL-2 based on information that was publicly available at the time of filing. Therefore, withdrawal of the objection to the specification is respectfully requested.

Priority

The Office Action alleges that "claims 12-73 do not properly benefit under 35 U.S.C. § 119(e) by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure" (Office Action, page 12). The Office Action concludes that "the effective filing date of the claims is deemed the filing date of the instant application, namely May 14, 2001." Applicants respectfully disagree.

Applicants submit that the claims, as currently amended, fully comply with the written description and enablement requirements of 35 U.S.C. § 112, first paragraph for the reasons discussed below. Therefore, the instant application is indeed entitled to the benefit of priority of U.S. provisional application 60/204,284, filed May 15, 2000.

Trademarks

The specification has been amended at page 29 to properly refer to Proleukin® with the appropriate symbol for a registered trademark.

35 U.S.C. § 112, first paragraph, Enablement

Claims 12-73 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide an enabling disclosure commensurate in scope with the claims. In particular, the Office Action alleges that "the specification, while being enabling for using a method for treating a patient diagnosed with breast cancer that overexpresses HER2 comprising administering to the patient a therapeutically effective amount of Herceptin™ (trastuzumab) or an immunotoxin comprised of a humanized version of murine antibody 4D5, murine antibody 520C9, or another anti-HER2 antibody, as taught by the prior art, in combination with a therapeutically effective amount of naturally occurring human IL-2, Proleukin™ (aldesleukin), or another recombinant human "IL-2" molecule effective to stimulate non-specific immune response in humans, as taught by the prior art, does not reasonably provide enablement for using a method for treating a subject having any cancer that is characterized by overexpression of HER2 according to the claims" (Office Action, pages 12-13). The Office Action states that the rejection is maintained allegedly because:

> The references cited in the preceding Office action (e.g., Stancovski et al; Lewis et al.) clearly indicate the skilled artisan cannot reliably and accurately predict which antibodies that binds the extracellular domain of HER2 ameliorate or aggravate disease symptoms in a subject afflicted with cancer, since it is not possible to predict which of such antibodies will inhibit or enhance the growth of cancer cells, and which will have no effect. Accordingly, the references indicate that merely knowing that a given antibody binds the extracellular domain of HER2 will not permit the skilled artisan to use the claimed invention to treat cancer in a subject, as it would first be necessary to determine if the antibody is effective to inhibit the growth of such cancer cells *in vivo*.
> (Office Action, page 14.)

The Office Action further alleges:

> Furthermore, the references cited in the preceding Office action clearly indicate that the skilled artisan cannot reliably and accurately predict which types of cancer characterized by the overexpression of HER2 can be treated using the claimed process, as it is not possible to predict which types of cancer overexpressing HER2 are "sensitive" to treatment with an anti-HER2 antibody that binds the extracellular domain of HER2.
> (Office Action, page 14.)

In addition the Office Action alleges:

> As evidenced by Lewis et al., for example, the skilled artisan cannot accurately and reliably predict which types of cancer can or cannot be treated using the claimed

> invention simply upon the basis of the level of expression of HER2. As such, for each and every type of cancer characterized as overexpressing HER2, other than such breast cancers, undue and/or unreasonable experimentation would have to be performed so as to determine if the claimed invention can be used to treat that type of cancer. (Office Action, page 18.)

The Office Action also alleges:

> As a new matter, with regard to claim 26, which is directed to the process of claim 12, wherein said dose of IL-2 or variant thereof is administered as a pharmaceutical composition selected from a group that includes a "lyophilized" composition and a "spray-dried" composition, the prior art does not appear to teach administering such compositions. Instead, the prior art teaches reconstituting such "dry" compositions in a pharmaceutically acceptable carrier for administration to the patient. The specification appears to be deficient therefore in teaching how such "dry" compositions are administered. (Office Action, page 22.)

Applicants respectfully traverse the rejection.

Applicants respectfully submit that the current claims indeed comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. In particular, claims 12, 16, 17, 42, and 63 have been amended to make explicit that the methods are directed to treating a subject for breast cancer. The Examiner has acknowledged that methods of treating breast cancer comprising concurrent therapy with an anti-HER2 antibody and IL-2 are enabled (see, *e.g.*, Office Action, page 12). In addition, claims 12, 16, 17, 42, and 63 have also been amended to make explicit that the anti-HER2 antibody or fragment thereof used in the claimed methods has anti-tumor activity and binds the same epitope as an anti-HER2 antibody selected from the group consisting of 4D5 and 520C9. Furthermore, the specification describes such anti-HER2 antibodies, which are known in the art to have anti-tumor activity in treatment of breast cancer (see specification, *e.g.*, at page 2, lines 19-25; and page 22, lines 11-16). The specification also discloses working examples for treatment of breast cancer according to the claimed methods (see, *e.g*, clinical study on treatment of breast cancer patients described in the specification at Example 1). Thus, the claims are adequately enabled by the specification.

With regard to the Examiner's assertion that methods of administration of lyophilized and spray-dried compositions of IL-2 are not enabled by the specification, nor taught in the prior art (Office Action, page 22), Applicants respectfully disagree. Methods are known in the art for administering such compositions either by reconstitution into a liquid or by pulmonary inhalation

of dry formulations (see specification, *e.g.*, at page 20, lines 16-22 and U.S. Patent Application Publication No. 2003/0198602 on methods for delivery of IL-2 by pulmonary inhalation, attached at Appendix A). Therefore, claim 26 is adequately enabled.

Availability of 4D5 and 520C9 Antibodies

In addition, the rejection of claims 25, 31, 52, 55, 58, 61, and 63-73 under 35 U.S.C. § 112, first paragraph, is maintained allegedly because Applicant has not provided the required assurance that the hybridoma cell lines, which produce the antibodies to which the claims refer have been deposited according to the provisions of the Budapest Treaty. The Office invites applicants to deposit the hybridomas in order to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

However, applicants reiterate that no deposit is necessary.

MPEP §2404.01 states:

> In an application where the invention required access to specific biological material, an applicant could show that the biological material is accessible because it is known and readily available to the public. The concepts of "known and readily available" are considered to reflect a level of public accessibility to a necessary component of an invention disclosure that is consistent with an ability to make and use the invention. To avoid the need for a deposit on this basis, the biological material must be both known and readily available - neither concept alone is sufficient. A material may be known in the sense that its existence has been published, but is not available to those who wish to obtain that particular known biological material. Likewise, a biological material may be available in the sense that those having possession of it would make it available upon request, but no one has been informed of its existence.

As discussed previously in the response to the Office Action of February 18, 2005, the 4D5 and 520C9 antibodies are **both** known and readily available to the public as required by MPEP §2404.01. The 4D5 (ATCC No. CRL-10463) and 520C9 (ATCC No. HB-8696) hybridomas are commercially available to the public without restriction from the American Type Culture Collection. According to the ATCC catalog available as of April 18, 2006, the 4D5 (CRL-10463) and the 520C9 hybridomas are available each for the purchase price of $330.00. The ATCC catalog is analogous to any other chemical

catalog that lists materials for purchase. In addition, Herceptin®, a humanized form of the 4D5 antibody, is also commercially available from Genentech. See the enclosed ATTC and Genentech product descriptions, attached at Appendix B). Thus, the requirements that the antibodies be known and readily available are satisfied.

For at least the above reasons, withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

35 U.S.C. § 112, second paragraph

Claims 28-31, 71, and 72 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." (Office Action, page 26).

(a) The Office Action alleges that claims 28-31 are indefinite in the recitation "said variant of human IL-2" because there is no antecedent basis in any of preceding claims 12, 26, and 27 (Office Action, page 26). To expedite prosecution, claim 28 has been amended to recite "said variant is des-alanyl-1, serine-125 human interleukin-2."

(b) The Office Action alleges that claim 71 is indefinite in the recitation "said introductory cycle" because there is no antecedent basis in preceding claim 63 (Office Action, page 27). To expedite prosecution, claim 71 has been amended to depend from claim 69.

(c) The Office Action alleges that claim 72 is indefinite in the recitation "said subsequent cycle" because there is no antecedent basis in preceding claim 63 (Office Action, page 3). To expedite prosecution, claim 72 has been amended to depend from claim 70.

For at least these reasons, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

35 U.S.C. § 112, first paragraph, New Matter

Claims 12-73 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (Office Action, page 27).

A. Recitation of an IL-2 Polypeptide Comprising SEQ ID NO:1 in Claims 12, 16, 17, 42, and 63

The Office Action alleges:

> Thus, while the inclusion of SEQ ID NO:1 in the claims finds support in the specification, as amended August 5, 2005, the original disclosure provides no apparent nexus between the amino acid sequence set forth as SEQ ID NO:1 and aldesleukin (i.e., des-alanyl-1, serine-125 human interleukin-2, or Proleukin™), which might serve as a basis for the amendment to the specification. If the amendment to the specification finds no written support in the specification including the claims, as originally filed, then amending the claims to recite "SEQ ID NO:1" introduces new matter and thereby violates the written description requirement set forth under 35 U.S.C. § 112, first paragraph. (Office Action, page 28.)

Applicants respectfully traverse the rejection under 35 U.S.C. § 112, first paragraph on the following grounds.

As discussed above regarding the objection under 35 U.S.C. § 132, the original disclosure of the specification does provide adequate descriptive support for SEQ ID NO:1 in the now revised Sequence Listing. At page 29, lines 2-7 of the specification, the sequence of aldesleukin is described as differing from the sequence of native human IL-2 in having the initial alanine residue eliminated and the cysteine residue at position 125 replaced by a serine residue. Given that the sequence of human IL-2 was well-known at the time of filing of the instant application (see, *e.g.*, see Figure 2b of U.S. Patent No. 4,738,927, which was cited in the instant application, for example, at page 17, line 13, and incorporated by reference; and GenBank Accession No. S82692), one of skill in the art would have understood that the sequence of aldesleukin was disclosed by this information. Furthermore, the sequence of aldesleukin is disclosed in the various references cited at page 17, lines 19-21 of the specification, which are incorporated by reference. Therefore, the specification adequately described the sequence of aldesleukin at the time of filing.

Nevertheless, in order to expedite prosecution Applicants have submitted a revised Sequence Listing containing a new SEQ ID NO:1 corresponding to the sequence of native mature human IL-2, as discussed above. Withdrawal of the new matter rejection under 35 U.S.C. § 112, first paragraph on this basis is therefore respectfully requested.

B. Recitation of Biologically Active Variants of IL-2 in Claims 12, 16, 17, and 42

The Office Action alleges:

> [I]t appears that the specification only provides written support for suitable biologically active variants of native and naturally occurring IL-2, including "fragments", analogues", and "muteins", as opposed to *variants of such variants*; see, in particular, page 13, lines 6 and 7. (Office Action, page 30.)

In addition, the Office Action alleges:

> [T]he specification, as originally filed, appears to only provide written support for a genus of variants of native and naturally occurring "IL-2" having an amino acid sequence that is at least 90% identical to the amino acid sequence [of] said "IL-2", which "retain the desired biological activity of the native polypeptide such that the pharmaceutical composition comprising the variant polypeptide has the same therapeutic effect as the pharmaceutical composition comprising the native polypeptide when administered to a subject" (page 12, lines 21-24; also see, e.g., page 13, lines 6 and 7; and page 14, lines 11-21. A variant of native "IL-2" is not equivalent to a variant of a polypeptide comprising SEQ ID NO:1; see, e.g., page 29, lines 2-7. Moreover, while the members of the genus of variants to which the claims are directed might be said to "retain the desired biological activity of the native polypeptide such that the pharmaceutical composition comprising the variant polypeptide has the same therapeutic effect as the pharmaceutical composition comprising the native polypeptide when administered to a subject", the specification, as originally filed, does not appear to describe such a genus of variants that activate NK cells, per se. (Office Action, pages 31-32).

As discussed above, SEQ ID NO:1 in the revised Sequence Listing now corresponds to the sequence of native mature human IL-2. As acknowledged by the Examiner, the specification does provide adequate support for variants of native human IL-2. See specification, for example, at page 12, lines 20-22; page 13, lines 6-7; and page 14, lines 11-17.

In order to expedite prosecution, claims 12, 16, 17, and 42 have been amended to make explicit that the variants of IL-2 have anti-tumor activity. By this amendment, Applicants expressly do not disclaim equivalents of the invention, which could include polypeptides having biological activities in addition to the recited anti-tumor activity. Applicants are amending the claims solely to obtain expeditious allowance of the instant application. Support for the amendment can be found in the specification, for example, at page 4, lines 11-22; page 6, lines 22-31; page 9, lines 27-31; page 12, lines 5-7 and 20-23; page 18, lines 6-10; page 26, lines 24-25.

For at least these reasons, withdrawal of the new matter rejections under 35 U.S.C. § 112, first paragraph is respectfully requested.

35 U.S.C. § 112, first paragraph, Written Description Rejection

Claims 12-73 have been rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of an adequate written description. In particular, the Office Action alleges:

> In this instance, there is no language that adequately describes the genus of anti-HER2 antibodies binding the extracellular domain of HER2, which when not conjugated to a cytotoxic moiety, inhibit the growth of cancer cells, so as to provide therapeutic benefit in treating cancer in a subject using the claimed invention. A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention. (Office Action, page 33.)

In addition, the Office Action alleges:

> Moreover, the specification does not describe the one, or possibly more "epitopes" to which the genus of antibodies must bind, if not conjugated to a cytotoxic moiety, so as to yield the claimed therapeutic effect *in vivo* during the practice of the claimed invention. (Office Action, page 35.)

The Office Action cites Jiang et al. (J. Biol. Chem. (2005) 280:4656-4662) as allegedly teaching that "different biological effects are associated with epitope specificity of the antibodies (Office Action, page 35). The Office Action further cites Reimer et al. (J. Immunol. (2004) 173:394-401) as allegedly teaching that "diverse biological effects that are exerted by different anti-HER2 antibodies depends upon epitope specificity" and Reimer et al. (Mol. Immunol. (2005) 42:1121-1124) as allegedly teaching that antibodies binding the same antigens have been shown to both ameliorate and aggravate disease symptoms" (Office Action, page 36). Applicants respectfully traverse the rejection on the following grounds.

Applicants respectfully submit that the claims, as amended, indeed comply with the written description requirement of 35 U.S.C. § 112, first paragraph. The pending claims are directed to methods of treating a subject for breast cancer characterized by overexpression of the HER2 receptor protein, comprising concurrent therapy with IL-2 and an anti-HER2 antibody or fragment thereof that has anti-tumor activity and binds the same epitope as a 4D5 or 520C9 anti-HER2 antibody. The Examiner has acknowledged that anti-HER2 antibodies with the specificity of the 4D5 antibody have been found to be effective in inhibiting growth of cancer cells (see

Office Action, page 35). Applicants direct the attention of the Examiner to the enclosed reference of Stockmeyer et al. (J. Immunol. (2003)171:5124-5129; attached at Appendix C), which shows that the unconjugated 520C9 antibody has been found to induce antibody-dependent apoptosis of human breast cancer cells. The specification describes such anti-HER2 antibodies, for example, at pages 22-25. Thus, the specification provides an adequate written description of the claimed invention.

For at least the above reasons, withdrawal of the written description rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

35 U.S.C. § 102

Claims 12-15, 17, 22-26, 35-37, 51, 52, 57, 58, 63, 64, 66, 68, and 73 have been rejected under 35 U.S.C. §102(b) as being anticipated by, Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999; hereinafter "Fleming") as evidenced by Fleming et al. (Clin. Cancer Res. (2002) 8:3718-3727). Fleming is cited for teaching a method of administering to patients a recombinant anti-HER2 monoclonal antibody in combination with IL-2 according to a dosage regimen, including IL-2 at a dose of 1.25 MIU/m^2 adminstered subcutaneously on a daily basis with intermediate-dose pulses of 15 MIU/m^2/day for 3 days every two weeks and anti-HER2 antibody at doses of 1, 2, and 4 mg/kg. Fleming also teaches reducing the dose of IL-2 to 1 MIU/m^2 daily with 12 MIU/m^2 pulses. Applicants respectfully traverse the rejection.

Applicants note that the priority date of the instant application is within one year of the ASCO 1999 meeting at which the Fleming et al. abstract was presented and subsequently published (see information on the ASCO 1999 meeting attached at Appendix D). Inventors Michael A. Caligiuri and Neal J. Meropol of the present application are coauthors on the Fleming et al. ASCO abstract and the relevant portions of Fleming et al. describe applicants' own work. The remaining co-authors on the abstract are not inventors of the claimed invention. To evidence this, applicants are submitting a Declaration of Michael Caligiuri, Neal J. Meropol and Richard L. Schilsky, pursuant to *In re Katz*. Thus, this basis for rejection has been overcome. Withdrawal thereof is respectfully requested.

35 U.S.C. § 103

A. Fleming in view of Meropol

Claims 27-31, 53, and 59 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) as evidenced by Fleming et al. (Clin. Cancer Res. (2002) 8:3718-3727) in view of Meropol et al. (Cancer Immunology & Immunotherapy (1998) 46:318-326). Applicants respectfully traverse the rejection.

As discussed above, Michael A. Caligiuri and Neal J. Meropol are coauthors on the Fleming et al. ASCO abstract. The relevant portions of Fleming et al. describe applicants' own work, and the remaining co-authors on the abstract are not inventors of the subject claims (see Declaration of Michael Caligiuri, Neal J. Meropol and Richard L. Schilsky, pursuant to *In re Katz*).

The secondary reference of Meropol fails to describe or suggest any method of treating cancer using an anti-HER2 antibody, let alone, any method of concurrent therapy using a combination of an anti-HER2 antibody and IL-2. Therefore, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

B. Fleming in view of U.S. Patent No. 4,863,726

Claims 27-31, 53, 59, and 65 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) as evidenced by Fleming et al. (Clin. Cancer Res. (2002) 8:3718-3727) in view of U.S. Patent No. 4,863,726. Applicants respectfully traverse the rejection.

Applicants reiterate that Michael A. Caligiuri and Neal J. Meropol are coauthors on the Fleming et al. ASCO abstract. The relevant portions of Fleming et al. describe applicants' own work, and the remaining co-authors on the abstract are not inventors of the subject claims (see Declaration of Michael Caligiuri, Neal J. Meropol and Richard L. Schilsky, pursuant to *In re Katz*).

The secondary reference of U.S. Patent No. 4,863,726 fails to describe or suggest any method of treating cancer using concurrent therapy with a combination of an anti-HER2

antibody and IL-2 administered according the claimed dosing regimens. Therefore, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

C. Fleming in view of U.S. Patent Application Publication No. 2003/0185796 A1

Claims 16, 32-34, 54, 55, 56, and 67 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) as evidenced by Fleming et al. (Clin. Cancer Res. (2002) 8:3718-3727) in view of U.S. Patent Publication No. 2003/0185796. Applicants respectfully traverse the rejection.

Applicants reiterate that Michael A. Caligiuri and Neal J. Meropol, are coauthors on the Fleming et al. ASCO abstract. The relevant portions of Fleming et al. describe applicants' own work, and the remaining co-authors on the abstract are not inventors of the subject claims (see Declaration of Michael Caligiuri, Neal J. Meropol and Richard L. Schilsky, pursuant to *In re Katz*).

The secondary reference of U.S. Patent Publication No. 2003/0185796 fails to describe or suggest any method of treating cancer using concurrent therapy with a combination of an anti-HER2 antibody and IL-2. Rather, U.S. Patent Publication No. 2003/0185796 pertains to methods of treating non-hodgkin's lymphoma with anti-CD20 antibodies. No mention is made of anti-HER2 antibodies. Therefore, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

D. Fleming in view of U.S. Patent Application Publication No. 2003/0185796 A1, further in view of Sosman

Claims 18, 19, 38-40, 42-47, 60-62, 69, and 70 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) as evidenced by Fleming et al. (Clin. Cancer Res. (2002) 8:3718-3727) in view of U.S. Patent Publication No. 2003/0185796, and further in view of Sosman et al. (J. Clin. Oncol. (1993) 11:1496-1505). Applicants respectfully traverse the rejection.

Applicants reiterate that Michael A. Caligiuri and Neal J. Meropol, are coauthors on the Fleming et al. ASCO abstract. The relevant portions of Fleming et al. describe applicants' own work, and the remaining co-authors on the abstract are not inventors of the subject claims (see Declaration of Michael Caligiuri, Neal J. Meropol and Richard L. Schilsky, pursuant to *In re Katz*).

As mentioned above, the secondary reference of U.S. Patent Publication No. 2003/0185796 fails to describe or suggest any method of treating cancer using concurrent therapy with a combination of an anti-HER2 antibody and IL-2. Sosman also fails to describe or suggest the claimed methods. Sosman pertains to methods of treating metastatic melanoma with anti-CD3 antibodies. No mention is made of anti-HER2 antibodies. Therefore, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

E. Fleming in view of U.S. Patent Application Publication No. 2003/0185796 A1

Claims 20, 21, 41, 48-50, 71, and 72 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Fleming et al. (Abstract No. 710, Program Proceedings, American Society of Clinical Oncology, 35th Annual Meeting, 1999) as evidenced by Fleming et al. (Clin. Cancer Res. (2002) 8:3718-3727) in view of U.S. Patent Publication No. 2003/0185796 and Sosman et al. (J. Clin. Oncol. (1993) 11:1496-1505, and further in view of Soiffer et al. Clin. Cancer Res. (1996) 2:493-499). Applicants respectfully traverse the rejection.

Applicants reiterate that Michael A. Caligiuri and Neal J. Meropol are coauthors on the Fleming et al. ASCO abstract. The relevant portions of Fleming et al. describe applicants' own work, and the remaining co-authors on the abstract are not inventors of the subject claims (see Declaration of Michael Caligiuri, Neal J. Meropol and Richard L. Schilsky, pursuant to *In re Katz*).

As discussed above, neither U.S. Patent Publication No. 2003/0185796 nor Sosman describe or suggest the claimed methods of treatment. Soiffer fails to describe or suggest any method of treating cancer using concurrent therapy with a combination of an anti-HER2 antibody and IL-2. Therefore, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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